Altered cognitive processes in the acute phase of mTBI: an analysis of independent components of event-related potentials

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Abstract: Mild traumatic brain injuries (mTBI) generate acute disruptions of brain function and a subset of patients shows persisting cognitive, affective, and somatic symptoms. Deficits in the executive function domain are among the more frequent cognitive impairments reported by mTBI patients. By means of independent component analysis, event-related potential components from a visual cued go/nogo task, namely contingent negative variation (CNV) and NoGo-P3, were decomposed into distinct independent components that have been shown to be associated with the executive processes of energization, monitoring, and task setting. A group of symptomatic mTBI patients was compared with a group of controls matched for sex, age, and education. Patients showed reduced amplitudes in the late CNV as well as in the early NoGo-P3 subcomponents. Whereas the decreased CNVlate component indicates an impaired ability to generate representations of stimulus-response associations and to energize the maintenance of response patterns, the reduced P3NOGOearly component suggests a deficient ability to invest attentional effort in the initiation of response patterns in mTBI patients. Besides indicating the effects of mTBI on cognitive brain processing, the results may open up the possibility for assessing individual mTBI profiles and facilitate personalized rehabilitative measures.

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Introduction

Mild traumatic brain injuries (mTBI) generate acute disruptions of brain function and, at the more severe end of the mTBI spectrum, brain structure [1]. It is assumed that at least 10% of mTBI patients show persisting cognitive, affective, and somatic symptoms [2]. These symptoms among other things include fatigue, sleep problems, irritability, feelings of depression, as well as attention problems and memory difficulties [3,4]. The latter, cognitive areas of impairment can be subsumed under the executive function domain and represent a substantial part of the persistent deficits reported following mTBI [5,6].

To date, neuropsychological assessment is one of the main clinical evaluation tools following mTBI [4]. However, in terms of ecological validity, certain cognitive problems may not be addressed by common neuropsychological methods [2]. Traditional measures such as reaction time are the result of a number of different processes involved in stimulus evaluation and response production. In contrast, event-related potentials (ERPs) provide a real-time measure of the neural events associated with such processes in different phases of a task. Therefore, ERP components can serve as physiological markers for specific cognitive processes [7].

In fact, ERPs have been shown to be useful in the assessment of sensory and cognitive processing capabilities in mTBI patients and thereby have shed light on the neurophysiological bases of covert cognitive dysfunctions associated with mTBI [3,8–10]. Broglio *et al.* [11] have shown reduced N2 and P3 amplitudes in athletes with a history of concussion. The ERPs were gained using a three-stimulus oddball task and the respective components presumably linked to the allocation of attentional resources and motor inhibition. No differences between mTBI and control groups were found on neuropsychological measures. Lachapelle *et al.* [12] used various ERP paradigms to evaluate visual and cognitive

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processing in mTBI patients. Compared with controls, the patients showed cognitive dysfunctions in higher-level processing, but no deficits in the processing of lower-level stimuli.

Because the underlying cognitive processes overlap both in space and in time, the ERP waveform represents the sum of activity from several sources [7]. Group independent component analysis (ICA) has been used successfully to extract the source signals underlying the measured multichannel signal mixtures on various occasions [13,14].

Brunner *et al.* [13] have shown that independent components (ICs) from a cued Go/NoGo paradigm can be associated with different functionally independent processes of the executive attention system. These processes comprise energization, monitoring, and task setting as operationalized in the 'ROBBIA' model [15]. Energization was described as the process of initiation and sustaining any response [16] or as the ability to voluntarily invest attentional effort to optimize behavior for achieving a goal [13]. Monitoring is needed in all nonroutine actions to control for making errors. Task setting is referred to as the process of acquiring the appropriate set of schemas [17].

In their study, Brunner *et al.* [13]. have decomposed the contingent negative variation (CNV) and the NoGo-P3 waves into four ICs. According to the conditions and time of occurring, these components were called IC $\mathrm{CNV}_{\mathrm{early}}$, IC $\mathrm{CNV}_{\mathrm{late}}$, IC $\mathrm{P3NOGO}_{\mathrm{early}}$, and IC $\mathrm{P3NOGO}_{\mathrm{late}}$. The amplitudes of the latter three proved to be specifically correlated with neuropsychological parameters sensitive to the functional domains of energization (IC $\mathrm{CNV}_{\mathrm{late}}$, $\mathrm{P3NOGO}_{\mathrm{early}}$), task setting (IC $\mathrm{CNV}_{\mathrm{late}}$), and monitoring (IC $\mathrm{P3NOGO}_{\mathrm{late}}$).

The main goal of the present study was to investigate the relationship between mTBI at the acute stage and a set of clearly defined processes of the executive attention system. We hypothesized that mTBI patients reporting at least a minimal amount of symptoms within the first week after injury would show deficits in attentional control as measured using ICs of ERPs. More specifically, we predicted that the amplitudes of three selected ERP components associated with the attentional processes of energization, monitoring, and task setting would be smaller compared with a control group matched for age, sex, and education.

Methods

Patients

Participants included 53 individuals (33 men, 20 women) with a diagnosis of mTBI and a healthy control group matched for sex, age, and education. The mean age of the participants was 34.10 years (SD = 12.59) in the mTBI group and 34.23 (SD = 12.21) in the control group. Time since injury was 5.33 days on average (SD = 1.60). The ERPs of one mTBI patient are not to be provided because of a technical problem. The patients were recruited in the emergency units of four hospitals in Switzerland. The injuries comprised sports/cycling accidents (45%), falls (23%), car/motorbike accidents (19%), accidents caused by falling objects (9%), and other accidents (4%). Inclusion criteria comprised the following: Glasgow Coma Scale score of 13–15 at hospital admission, normal post-traumatic computed tomography, and at least one of the following characteristics: loss of consciousness up to 30 min, presence of an alteration of mental state such as confusion, disorientation or dizziness at the time of the incident, post-traumatic amnesia less than 60 min, and/or retrograde amnesia less than 30 min. The exclusion criteria were a history of neurologic disease, psychiatric disease, or neurosurgery, as well as earlier TBI, current and past drug or alcohol abuse, and age younger than 17 or older than 64 years.

The analyses were carried out using a downsized sample of 32 trauma patients who reported clinical impairments at the time of data collection. The reasons for this are as follows: there is a large overlap in the low severity range among the self-reported symptoms of the two participant groups and it is supposable that mTBI patients reporting symptoms in a comparable degree to controls in the acute state may not show any brain functional deficits. Furthermore, from a clinical point of view, mTBI patients with no symptoms are not in focus. The downsized sample is composed of mTBI patients with a Rivermead Post Concussion Symptoms Questionnaire score (RPQ; see the Procedure section) equal to or higher than 10 and the matching controls.

The study was approved by the local ethics committee and written informed consent was obtained from the participants before study intake. The participants were reimbursed for their income lost because of study participation.

Procedure

This paper is part of a longitudinal and interdisciplinary study comprising three measurement points and different neuroimaging methods. The data reported in this paper cover the ERP assessment at the acute stage of the mTBI. All patients were tested within 8 days after injury. A series of neuropsychological tests and self-report questionnaires were administered to the participants. With one exception, these instruments are not relevant to this paper. The RPQ [18] was used to measure the severity of commonly reported physical, cognitive, and emotional postconcussion symptoms. The 16 items can be answered on a five-point scale within a range of 0 (not experienced at all) to 4 (a severe problem). RPQ sum scores were calculated excluding scores of 1 (no more of a problem).

Behavioral task

In the cued Go/NoGo task, three categories of visual stimuli (pictures of animals, plants, and people) are presented in a total of 300 trials. Each trial consists of the presentation of a pair of stimuli. The trials were grouped into four categories: animal-animal (Go trials), animal-plant (NoGo trials), plant-plant (ignore trials), and plant-human (novel trials). Each stimulus was presented with a duration of 100 ms and the interstimulus interval within each trial was 1000 ms. The trials were grouped into four blocks, and each block consisted of a pseudorandom presentation of 100 trials with equal probability for each trial category. The participants were instructed to press a button as fast as possible in response to all Go trials using the index finger of the right hand. Go and NoGo trials both start with a picture of an animal (cue) and participants are supposed to prepare to respond. These conditions are referred to as 'cue conditions'. During the task, the participants were seating in a comfortable chair and looking at a 17-inch computer screen at a distance of 1.5 m.

EEG acquisition and preprocessing

The electroencephalogram (EEG) was recorded using a Mitsar 201 (Mitsar Co. Ltd., St Petersburg, Russian Federation) and sampled at 250 Hz. The electrodes were placed according to the International 10–20 system using caps with 19 tin electrodes (Electro-cap International Inc., Eaton, Ohio, USA). Reference electrodes were placed at the earlobes. The EEG was bandpass and notch filtered (0.53–50 and 45–55 Hz, respectively) and montage was changed to average montage before data processing. Eyeblink and horizontal eye movement artifacts were corrected by zeroing the activation curves of individual ICA components corresponding to eyeblinks and horizontal eye movements [19]. In addition, epochs of the filtered EEG with excessive amplitude (>100 μV) and/or excessive (threshold = z-score of 6) 0 to 3 Hz and 20 to 50 Hz band frequency activities were automatically excluded from further analysis.

Decomposition of ERPs into independent components

The ICA Infomax algorithm [20] was applied to the collection of ERPs from the entire sample of 106 participants. ICA was performed using the EEGLAB Matlab toolbox [21]. ICA input data are the two-dimensional 19-scalp-locations × 106-ERP-time-series matrix. To detect the independent CNV_{late} component, ICA was applied to the time interval between the first and the second stimulus (1100 ms) of the cue condition trials. To detect the independent $P3NOGO_{early}$ and $P3NOGO_{late}$ components, ICA was applied to the 700 ms time interval after the second stimulus of the NoGo trials. Subsequently, the resulting spatial filters were applied to the individual ERPs. ERPs were then back-projected to the electrode with the highest activation of the component.

Extraction of ERP features

The individual ERP features were quantified by measuring the mean amplitudes. First, the independent ERP epochs were baseline corrected using the 100 ms prestimulus period. Trials with omission or commission errors were excluded from averaging. The amplitudes of the $P3NOGO_{early}$ and $P3NOGO_{late}$ components were measured by identifying the positive extremum in the latency range of 250–370 and 290–470 ms, respectively. Subsequently, the area under the curve in an 80 ms time window centered at the individual extremum was calculated and converted into a mean amplitude measure. Because of the low frequency of the wave and following the procedure of Brunner *et al.* [13], we used the last 100 ms before the occurrence of the second stimulus to compute the area amplitude of the IC CNV_{late}. This amplitude was converted into a mean amplitude measure as well.

Statistics

Statistical analyses were carried out using SPSS for Windows, version 17 (SPSS Inc., Chicago, Illinois, USA). The group comparisons were performed with a downsized sample ($n = 32$ per group). Categorical demographic data group comparisons were performed using McNemar tests. Interval-scaled demographic data, behavioral data, and ERP data group comparisons were analyzed using paired-sample t-tests. The level of significance was set to $\alpha = 0.05$ and the P-values, unless otherwise indicated, were adjusted using Holm–Bonferroni sequential correction [22].

Results

Table 1 shows the demographic data and the RPQ sum scores of the downsized sample. Time since injury in the downsized patient group was 5.23 days (SD = 1.56, range = 1.63–8.24).

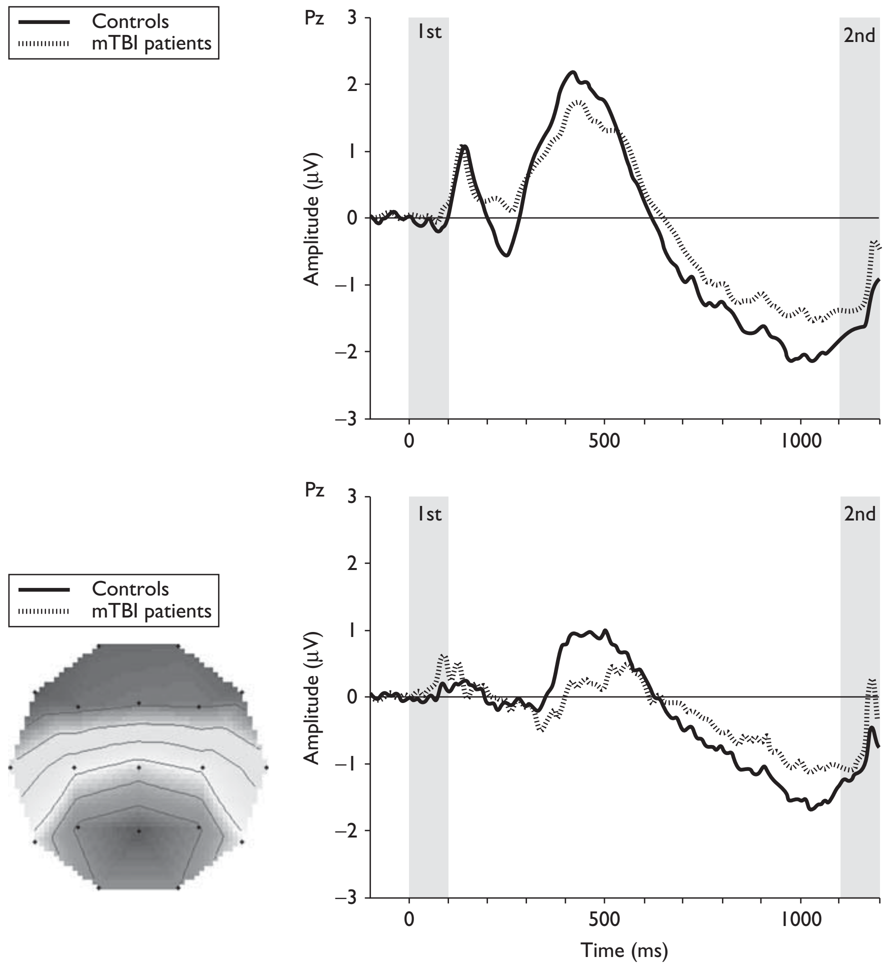
The topography and the activation curve of IC CNV_{late} are presented in Fig. 1. The component shows a distinctive negativity preceding the onset of the second stimulus and has a parietal distribution. The topographies and activation curves of the NoGo-P3-related ICs are presented in Fig. 2. The IC $P3NOGO_{early}$ is

Table 1 Demographics and RPQ sum scores of the downsized sample

	mTBI patients			Controls			*P* value
N	32			32			
Sex (female/male)	18/14			18/14			1.000
Handedness (l/r)	3/29			5/27			0.687
	Mean	SD	Range	Mean	SD	Range	
Age	34.69	13.19	17–57	34.75	13.12	17–57	0.850
Years of education	11.59	2.47	8–18	12.16	2.02	7–18	0.071
RPQ sum score	21.47	9.28	10–46	2.56	3.87	0–14	< 0.001*

RPQ, Rivermead Post Concussion Symptoms Questionnaire score.
*Significant difference between groups.

Fig. 1



Top: Original grand average ERP waves at Pz electrode, shown separately for the mTBI and the control subsamples. Bottom left: Topography of IC CNV_{late}. Bottom right: Activation curves of IC CNV_{late}, back-projected to Pz electrode and shown separately for the mTBI and the control subsamples. *Y*-axis – amplitude in μV. *X*-axis – time relative to onset of stimulus 1. Grey bars indicate the appearance of the stimuli. CNV, contingent negative variation; ERP, event-related potential; IC, independent component; mTBI, mild traumatic brain injury.

characterized by a positive deflection peaking around 310 ms after the onset of stimulus 2 and a central distribution. The IC $P3NOGO_{late}$ shows a positive peak around 380 ms poststimulus 2 and has a central distribution as well.

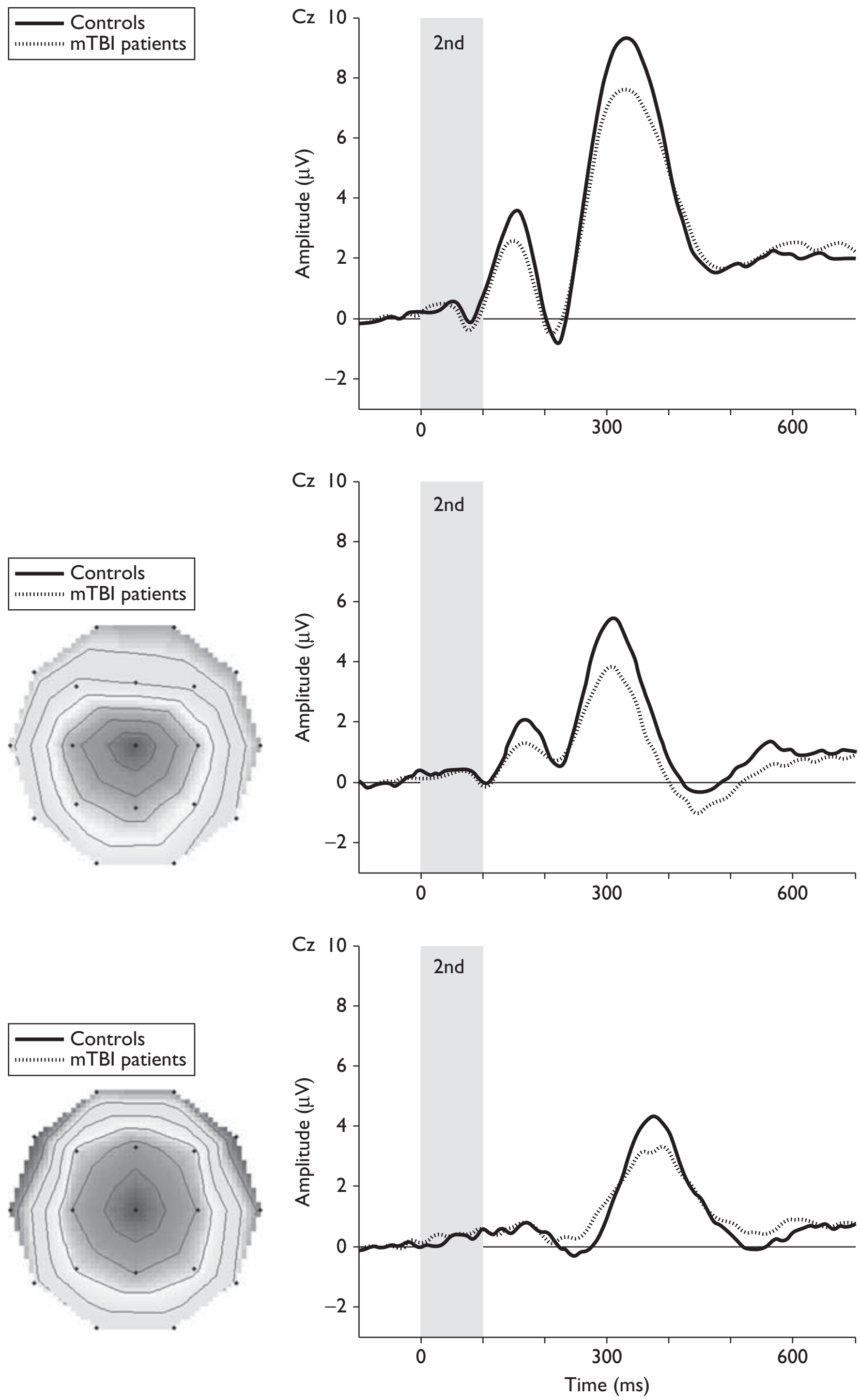
Mean amplitude data of the downsized sample are presented in Table 2. The mean amplitudes of the ICs CNV_{late} [$t(31)=2.789$, $P=0.024$] and $P3NOGO_{early}$ [$t(31)=-2.829$, $P=0.024$] were significantly reduced in mTBI patients when compared with the controls. No group difference was found for IC $P3NOGO_{late}$ n[$t(31)=-1.046$, $P=0.304$].

Discussion

The main goal of the present study was to investigate the consequences of mTBI on cognitive processing within a framework of specific functions of the anterior attentional system [16]. Specifically, we examined whether ERP components associated with the frontal lobe processes of energization, monitoring, and task setting differ between healthy controls and mTBI patients reporting at least minimal symptoms within 1 week after injury. The close connection between ERP components and the specific executive processes was established by decomposing the ERP waves into ICs. Associations between these ICs and the above-mentioned executive processes had formerly been established by correlating the component's amplitudes with neuropsychological test scores [13].

In fact, mTBI patients showed smaller amplitudes on the ICs CNV_{late} and $P3NOGO_{early}$ compared with the controls. Smaller ERP amplitudes in TBI patients are a common finding [23] and suggest a diminished degree of engagement of the underlying cognitive process [7]. Thus, as a main finding, the results indicate an

Fig. 2



Top: Original grand average ERP waves at Cz electrode, shown separately for the mTBI and control subsamples. Mid left: Topography of IC P3NOGO$_{early}$. Mid right: Activation curves of IC P3NOGO$_{early}$, back-projected to Cz electrode and shown separately for the mTBI and control subsamples. Bottom left: Topography of IC P3NOGO$_{late}$. Bottom right: Activation curves of IC P3NOGO$_{late}$, back-projected to Cz electrode and shown separately for the mTBI and control subsamples. *Y*-axis – amplitude in μV. *X*-axis – time relative to onset of stimulus 2. Grey bars indicate the appearance of stimulus 2. ERP, event-related potential; IC, independent component; mTBI, mild traumatic brain injury.

impairment in the ability to energize the initiation and maintenance of response patterns as well as in the ability to generate representations of stimulus–response associations in the acute phase of mTBI in clinically symptomatic patients. As mTBI patients who fully recover 1 week after injury are not of primary interest for

Table 2 Mean ERP amplitudes of the downsized sample

	mTBI patients		Controls			
	Mean	SD	Mean	SD	*P* value	Corrected *P* value
IC CNV_{late} amplitude (μV)	−1.06	1.08	−1.56	1.08	0.009	0.024*
IC $P3NOGO_{early}$ amplitude (μV)	3.68	2.74	5.21	3.15	0.008	0.024*
IC $P3NOGO_{late}$ amplitude (μV)	3.79	2.89	4.37	2.48	0.304	0.304

CNV, contingent negative variation; ERP, event-related potential; IC, independent component; mTBI, mild traumatic brain injury.
*Significant difference between groups.

clinicians, we focused on patients who report a certain amount of typical postconcussion symptoms. Symptom-free mTBI patients were not analyzed.

Besides clarifying the effects of mTBI on information processing, the evaluation of ERPs by means of ICs that are embedded in a well-grounded theoretical model serves a further purpose. Assessment of distinct cognitive brain processes may increase the understanding of individual mTBI profiles and facilitate personalized rehabilitative measures.

Conclusion

This study shows that patients show altered electrophysiological markers of cognition in the acute stage after mTBI. Independent ERP components represent an easily manageable neuroimaging method that can complement traditional neuropsychological assessment by revealing the subtle and individual cognitive deficits of mTBI patients and can therefore facilitate personalized rehabilitation.

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Conflicts of interest

S.J. was the PI of the study and is medical director of the Bellikon Rehabilitation Clinic, owned by SUVA. P.D. received financial support from SUVA. The views expressed are those of the authors and not necessarily those of the SUVA. A.M. is a member of the management board of HBImed AG. For the remaining authors there are no conflicts of interest.

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